

**IN THE SPECIFICATION:**

Please amend the specification as follows:

Please amend page 2, lines 4-8, as follows:

C2  
--According to this invention, a modified FVIII cDNA is made available in which the B-domain of the wild-type FVIII cDNA has been deleted and a truncated FIX intron 1 has been inserted in one or more locations of the FVIII cDNA. In addition the B-domain of the wild-type FVIII cDNA has been replaced by four arginines.--

Please insert the following on page 2, following line 8:

C3  
sub D2  
--BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Schematic view of the Factor IX intron I inserted in the Factor VIII intron 1 location.

FIG. 2. Cloning Strategy of Factor IX intron 1 in Factor VIII introns 12 and 13 locations.

FIG. 3. Kinetic Factor VIII production from different transfected cell lines.

FIG. 4. Procoagulant activities from different transfected cell supernatants.

FIG. 5. Factor VIII antigen production in a Hep G2 cell line.

FIG. 6. Quantitative analysis of Factor VIII mRNA in transfected Chinese Hamster Ovary cells.

FIG. 7. Intracellular amount of Factor VIII in different cell lines.--

Please replace page 3, lines 9 through 11, with the following:

--WT sequence: TAA GTC ATG CAA ATA (SEQ. ID NO. 10)

FINNEGAN  
HENDERSON  
FARABOW  
GARRETT &  
DUNN LLP

1300 I Street, NW  
Washington, DC 20005  
202.408.4000  
Fax 202.408.4400  
www.finnegan.com

C4  
concord

Kozak modified: ACA **CCC** ATG GAA ATA (SEQ. ID No. 11)

The modified nucleic acids are represented in bold.--

Please replace page 4, lines 1 through 13, with the following:

Sub D3  
Ch

--Four arginines replace according to the invention the B-domain of the FVIII protein. They are introduced by the oligonucleotides used for the cloning of the two fragments surrounding the B-domain (see Fragments 2 and 3 of Table 1), namely the oligonucleotides 4R AS (SEQ. ID No. 4) and 4R S (SEQ. ID No. 5). The Sal I site was generated by the coding sequence of the arginines as follows:

SAL I SITE

4R S :5'-A AGA CGT CGA CGA GAA ATA ACT CGT ACT ACT CTT

(SEQ. ID No. 5)

4R AS TTG TTA CGG TAA CTT GGT TCT GCA GCT GCT CTT (SEQ. ID

No. 4)

CORRESPONDING PEPTIDIC SEQUENCE:

Pro Arg Arg Arg Arg Glu Ile Thr Arg Thr Thr Leu (SEQ. ID No. 12)

In the wild-type FVIII the peptidic sequence is:

Pro-Arg-Domain B-Arg-Glu (SEQ ID No. 13)--

Please replace page 5, lines 11 through 13, with the following:

C6

--According to the invention, the FVIII cDNA was further modified by the insertion of a Factor IX truncated intron 1 (FIX TI1) ( SEQ. ID No. 9). The FIXTI 1 was inserted in different locations of the FVIII cDNA as follows: --

FINNEGAN  
HENDERSON  
FARABOW  
GARRETT &  
DUNNER LLP

1300 I Street, NW  
Washington, DC 20005  
202.408.4000  
Fax 202.408.4400  
www.finnegan.com

Please replace page 6, lines 1 through 5, with the following:

CA  
D4

--The FIX T11 sequence (SEQ. ID No. 9) used according to the invention in different locations of the FVIII cDNA starts after the coding sequence by the splice donor sequence and ends by the splice acceptor sequence of the truncated intron 1. The upper case letters start after and stop before the Nsi I and Mlu I restriction sites, respectively.--

Please replace page 6, lines 10 through 22, with the following:

C8

--A similar strategy was used for inserting the three FIX T11 in different locations. In each case three PCR fragments (A,B,C) were generated with the Expand system using Factor VIII cDNA as a template for the segments A and C, and Factor IX intron 1 for the B fragment. The A fragment extremities comprise Factor VIII sequence on the 5' end, and on the 3' end a fusion between the FVIII 3' splicing sequence and the Factor IX first intron 5' splicing sequence. A Nsi I restriction site was added between these two sequences. The B fragment possesses at the 5' extremity a complementary sequence to the previous fragment, the truncated Factor IX intron 1, and at the 3' end and inserted Mlu I restriction site. The C fragment was made of the complementary sequence of the 3' extremity from fragment B followed by the Factor IX first intron 3' splicing sequence and by the Factor VIII cDNA downstream coding sequence (see Figure 1).--

Please replace page 11, lines 2 through 21, with the following:

FINNEGAN  
HENDERSON  
FARABOW  
GARRETT &  
DUNNER LLP

1300 I Street, NW  
Washington, DC 20005  
202.408.4000  
Fax 202.408.4400  
www.finnegan.com

C<sup>9</sup>

--A sheep anti-FVIII antibody from Cedarlane (Hornby, Canada) was purchased and positively tested in a control immunoblot using recombinant FVIII. This antibody was used in an immunoblot on cell supernatant but no signal was obtained due to the low amount of secreted antigen. An immunoprecipitation was done on cell supernatant but here again no signal was obtained indicating the inability of this antibody to immunoprecipitate FVIII. An immunoblot was done on Triton-X100 soluble cell lysates. 90mm dishes were lysed with 300 ml ice-cold lysis buffer (Hepes 20 mM pH7.5, KCl 100mM, MgCl<sub>2</sub> 2mM, Triton-X 100 0.5 %). Cells were scraped and centrifuged at 4 C, 10 min at 14000g. Protein concentration was measured with the Dc-protein Assay kit (BioRad, Hercules, USA). 175 g of each cell lysate were loaded on a 7.5% acrylamide gel and treated following the Laemmli protocol. After semi-dry transfer (35 min at 400mA), the nitrocellulose membrane was incubated overnight in TBS-T (20 mM Tris pH 7.5, NaCl 0.15 M, Tween-20 0.5%). The membrane was then incubated 1 h with the anti-FVIII antibody (5 g/ml) in TBS-T. After three washes of 10 min each in TBS-T, the membrane was incubated for 30 min with a rabbit anti-sheep peroxidase coupled antibody (dilution 10<sup>-4</sup> in TBS-T). Extensive washes were conducted before revelation with the ECL system (Amersham).--

Please replace page 12, lines 3 through 19, with the following:

C<sup>10</sup>

--Subjects of the invention are, therefore, FVIII-B-domain deleted constructs containing a slightly modified Factor IX truncated intron I in different locations of the cDNA. Among these constructs a cDNA bearing the truncated intron I in both

FINNEGAN  
HENDERSON  
FARABOW  
GARRETT &  
DUNNER LLP

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Washington, DC 20005  
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www.finnegan.com